

REMARKS/ARGUMENTS

Upon entry of the present Amendment, claims 31-50 are pending and are currently under examination; claims 1-30 and 51-52 have been canceled without disclaimer or prejudice to renewal; and claims 31, 34, 43, 45 and 49 have been amended. Support for the amendments to claims 31, 34, 43, 45 and 49 can be found throughout the specification and claims as originally filed and, thus, no new matter has been introduced. Reconsideration is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 31-50 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner's concerns and, in turn, Applicants responses to those concerns are set forth below.

a. The Examiner has rejected claims 31, stating that it is unclear how hydrophilic compounds can be present in the lipid phase.

It is Applicants' understanding that the mucoadhesive compounds disclosed in the specification and claims would reside at the interface of the water and lipid, and that they would be intercalated with the phospholipid. As such, claim 31 is not unclear. Accordingly, Applicants respectfully request that the Examiner withdrawn this portion of the § 112, second paragraph, rejection.

b. The Examiner has rejected claims 34 and 49 as allegedly indefinite, stating that "[r]eciting the term 'syndromes including' in a Markush format in claims 34 and 49 is improper.

In order to expedite prosecution, Applicants have amended claims 34 and 49 to remove the phrase "masquerade syndromes including" from both claims 34 and 49. In view of the amendments to claims 34 and 49, the Examiner's concern is overcome. Accordingly, Applicants respectfully request that the Examiner withdrawn this portion of the § 112, second paragraph, rejection.

Rejections Under 35 U.S.C. § 102(b)

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features, or limitations of the presently claimed invention.

Rejection Under 35 U.S.C. § 102(b) Over Guo

Claims 31, 33, 34, 37, 40, 43, 45 and 49 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Guo (U.S. Patent No. 4,804,539). In support of this rejection, the Office Action states that "Guo discloses a method of ocular delivery of ophthalmic drugs for the treatment of eye conditions using cationic liposomes" (see, page 3 of the Office Action). To the extent this rejection is applicable to the amended claims, Applicants respectfully traverse this rejection.

As amended, independent claim 31 recites:

A method of treating an ophthalmic disorder in a mammal, said method comprising administering to the eye of said mammal a lipid formulation, said lipid formulation comprising: a lipid phase, said lipid phase comprising a neutral lipid and a modifying agent selected from the group consisting of cationic lipids and mucoadhesive compounds; an aqueous phase; and a therapeutic agent, wherein said therapeutic agent in said lipid formulation is useful for treating said ophthalmic disorder; wherein said lipid formulation comprises about 0.001 to about 10.000 wt % of said lipid phase and about 90.000 wt % to about 99.999 wt

% of said aqueous phase, and wherein said lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10% modifying agents and 0.1 to 10 wt% antioxidant.

Similarly, as amended, independent claim 43 recites:

A method for treating or preventing ocular inflammation, paracentesis-induced miosis, cystoid macular edema and mydriasis, said method comprising administering a therapeutically effective amount of one or more non-steroidal anti-inflammatory drugs encapsulated or contained within a liposome formulation, said liposome formulation comprising 0.001 to 10.000 wt% lipid phase, and 90.000 to 99.999 wt% aqueous phase, wherein said lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10% modifying agents and 0.1 to 10 wt% antioxidant.

Applicants respectfully submit that Guo does not teach or suggest a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of said lipid phase and about 90.000 wt % to about 99.999 wt % of said aqueous phase, wherein said lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt% modifying agents (*i.e.*, cationic lipid or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. In stark contrast, a perusal of the Guo patent reveals that the lipid phase of the liposome compositions disclosed therein comprises 40 to 80 mole percent of neutral lipid and 20 to 60 mole percent of cationic lipid. Accordingly, Guo did not anticipate the presently claimed methods and, thus, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under 35 U.S.C. § 102(b) Over Szulc *et al.*

Claims 31 and 40 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Szulc *et al.* (Farm. Pol. 1988). In support of this rejection, the Office Action states that "Szulc *et al.* disclose a method of decreasing intraocular pressure using cationic liposomes containing pilocarpine. The liposomes contain lecithin, cholesterol and stearylamine (English abstract)" (*see*, page 3 of the Office Action). To the extent this rejection is applicable to the amended claims, Applicants respectfully traverse this rejection.

As with the Guo patent, Applicants respectfully submit that Szulc *et al.* do not teach or suggest a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of

said lipid phase and about 90.000 wt % to about 99.999 wt % of said aqueous phase, wherein said lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Absent such a teaching, the Szulc *et al.* reference did not anticipate the presently claimed methods and, thus, they are novel over the teachings of Szulc *et al.* Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejections Under 35 U.S.C. § 103

As set forth in M.P.E.P. § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Therefore, in order to establish a *prima facie* case, all three criteria must be met.

Rejection Under 35 U.S.C. § 103(a) Over Guo

Claims 32, 34-36, 38-39, 41-42, 44, 46-48 and 50 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Guo (U.S. Patent No. 4,804,539).

As set forth above, both independent claims 31 and 43 recite the use of a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of a lipid phase and about 90.000 wt % to about 99.999 wt % of an aqueous phase, wherein the lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Applicants respectfully submit that Guo does *not* teach or suggest the lipid formulation or liposome used in the presently claimed methods. Thus, as pointed out by the Examiner, in addition to failing to teach the specifically claimed anti-inflammatory agents and the eye conditions that result in the inflammatory conditions, Guo also

fails to teach or suggest the presently claimed lipid formulations or liposomes. Absent such teachings or suggestions in Guo, the presently claimed methods are non-obvious and, thus, patentable over Guo. Accordingly, Applicants urge the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. § 103(a) Over Guo in view of Touitou

Claims 32, 34-36, 38-39, 41-42, 44, 46-48 and 50 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Guo (U.S. Patent No. 4,804,539) cited above, further in view of Touitou (U.S. Patent No. 5,716,638).

As set forth above, both independent claims 31 and 43 recite the use of a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of a lipid phase and about 90.000 wt % to about 99.999 wt % of an aqueous phase, wherein the lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Applicants respectfully submit that Guo in combination with Touitou does **not** teach or suggest the lipid formulation or liposome used in the presently claimed methods. Thus, although Touitou may disclose diclofenac, both Guo and Touitou fail to teach or suggest the presently claimed lipid formulations or liposomes. Absent such teachings or suggestions in Guo and Touitou, the presently claimed methods are non-obvious and, thus, patentable over the combination of Guo and Touitou. Accordingly, Applicants urge the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. § 103(a) Over Guo in view of Malerhofer

Claims 41-42 and 46-48 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Guo (U.S. Patent No. 4,804,539) cited above, further in view of Malerhofer (U.S. Patent No. 5,853,753) or vice versa.

As set forth above, both independent claims 31 and 43 recite the use of a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of a lipid phase and about 90.000 wt % to about 99.999 wt % of an aqueous phase, wherein the lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Applicants respectfully submit that Guo in combination with Malerhofer does **not** teach or suggest the lipid formulation or liposome used in

the presently claimed methods. Thus, although Malerhofer may disclose liposome formulations containing active agents for the treatment of eye diseases of allergic or viral etiology, both Guo and Malerhofer fail to teach or suggest the presently claimed lipid formulations or liposomes. Absent such teachings or suggestions in Guo and Malerhofer, the presently claimed methods are non-obvious and, thus, patentable over the combination of Guo and Malerhofer. Accordingly, Applicants urge the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. § 103(a) Over Schaeffer in view of Malerhofer

Claims 31-50 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Schaeffer (*Invest. Ophthalmol. Vis. Sci.*, 1982) by itself or further in view of Malerhofer (U.S. Patent No. 5,853,753).

As set forth above, both independent claims 31 and 43 recite the use of a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of a lipid phase and about 90.000 wt % to about 99.999 wt % of an aqueous phase, wherein the lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Applicants respectfully submit that Schaeffer in combination with Malerhofer does **not** teach or suggest the presently claimed methods or the lipid formulation or liposome used in the presently claimed methods. Moreover, as pointed out by the Examiner, Schaeffer does not teach or suggest the encapsulation of the presently claimed drugs or the treatment of the specifically claimed diseases. Malerhofer does not cure the deficiencies of Schaeffer. Schaeffer and Malerhofer, either alone or together, amount to no more than an invitation to experiment,

Absent such teachings or suggestions in Schaeffer and Malerhofer directed to the presently claimed lipid formulations and liposomes, the presently claimed methods are non-obvious and, thus, patentable over the combination of Schaeffer and Malerhofer. Accordingly, Applicants urge the Examiner to withdraw this rejection.

Rejection Under 35 U.S.C. § 103(a) Over Schaeffer in view of Malerhofer and Touitou

Claims 41-42 and 46-48 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Schaeffer (*Invest. Ophthalmol. Vis. Sci.*, 1982) by itself or further in view of Malerhofer (U.S. Patent No. 5,853,753) as set forth above, further in view of Touitou (U.S. Patent No. 5,716,638) cited above.

As set forth above, both independent claims 31 and 43 from which claims 41-42 and 46-48, respectively, depend, recite the use of a lipid formulation or liposome comprising about 0.001 to about 10.000 wt % of a lipid phase and about 90.000 wt % to about 99.999 wt % of an aqueous phase, wherein the lipid phase comprises 0.01 to 10 wt% phospholipid, 0.1 to 10 wt % modifying agents (*i.e.*, cationic lipids or mucoadhesive compounds) and 0.1 to 10 wt% antioxidant. Applicants respectfully submit that Schaeffer in combination with Malerhofer does **not** teach or suggest the presently claimed methods of the lipid formulation or liposome used in the presently claimed methods. Moreover, as pointed out by the Examiner, Schaeffer and Malerhofer do not teach or suggest the encapsulation of the anti-inflammatory drug diclofenac. Touitou does not cure the deficiencies of Schaeffer and Malerhofer. Touitou may disclose diclofenac, but it does not teach or suggest the lipid formulations and liposomes of the present invention. Again, the cited references, either alone or together, amount to no more than an invitation to experiment,

Absent such teachings or suggestions in Schaeffer, Malerhofer and Touitou directed to the presently claimed lipid formulations and liposomes, the presently claimed methods are non-obvious and, thus, patentable over Schaeffer, Malerhofer and Touitou. Accordingly, Applicants urge the Examiner to withdraw this rejection.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw all of the § 103 obviousness rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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